

(19) World Intellectual Property  
Organization  
International Bureau



(43) International Publication Date  
12 August 2004 (12.08.2004)

PCT

(10) International Publication Number  
**WO 2004/067004 A1**

(51) International Patent Classification<sup>7</sup>: **A61K 31/4468**

(74) Agents: **ZACCO SWEDEN AB** et al.; Box 23101, S-104 35 Stockholm (SE).

(21) International Application Number:

PCT/SE2004/000037

(22) International Filing Date: 15 January 2004 (15.01.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/443,857 31 January 2003 (31.01.2003) US

(71) Applicant (for all designated States except US): **OREXO AB** [SE/SE]; Box 303, S-751 05 Uppsala (SE).

(72) Inventors; and

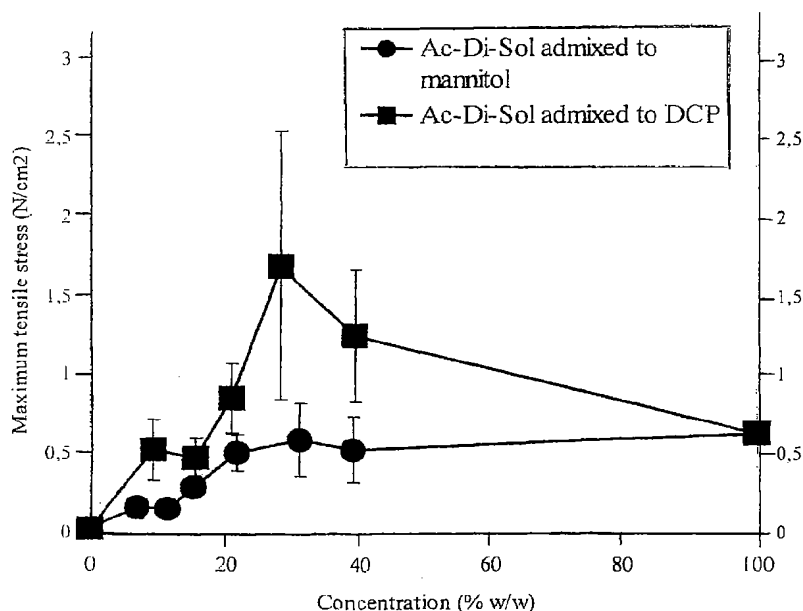
(75) Inventors/Applicants (for US only): **NYSTRÖM, Christer** [SE/SE]; Holmvägen 22 B, S-756 61 Uppsala (SE). **BREDENBERG, Susanne** [SE/SE]; Sveavägen 87, S-113 50 Stockholm (SE).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK,

[Continued on next page]

(54) Title: A RAPID-ACTING PHARMACEUTICAL COMPOSITION



Maximum tensile stress in detaching powder specimens from mucus membrane as a function of concentration of milled Ac-Di-Sol mixed with Mannitol or DCP. Mean values  $\pm$  S.D.

(57) Abstract: A pharmaceutical composition for the treatment of acute disorders is described. The composition comprises an essentially water-free, ordered mixture of at least one pharmaceutically active agent in the form of microparticles which are adhered to the surfaces of carrier particles which are substantially larger than the particles of the active agent or agents, and are essentially insoluble or sparingly soluble in water, in combination with a bioadhesion and/or mucoadhesion promoting agent adhered to the surfaces of said carrier particles. The composition is primarily intended for sublingual or intranasal administration. The invention also relates to a method for preparing the composition and to the use of the composition for the treatment of acute disorders.



TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

**Published:**

— *with international search report*

**A rapid-acting pharmaceutical composition****Field of the invention**

5 The present invention relates to a rapidly acting pharmaceutical composition for sublingual or intranasal administration of a pharmaceutical agent, to a method for preparing such a composition, and to a method for the treatment of acute disorders by the use of such a composition.

**10 Background of the invention**

Acute and/or severe disorders are a common cause of emergency treatment or hospitalization. One of the most common disorders of this type is acute or breakthrough pain. In cancer patients, pain is usually treated with non-steroid anti-inflammatory drugs (NSAIDs) and opiates alone or in combination. Opioid-requiring cancer pain patients are usually given slow-release opiates (slow-release morphine or ketobemidone or transdermal fentanyl). A characteristic feature of cancer pain are periods of inadequate analgesia (breakthrough pain). Most often they are due to increased physical activity of the patient. However, treatment of breakthrough pain by administration of increased time contingent doses of long-acting analgesics causes adverse side effects such as excess sedation, nausea, and constipation.

Other disorders and conditions which require a fast-acting treatment are, for example, pulmonary edema, gastroesophageal reflux, insomnia and nephrolithiasis.

25 Presently available oral, rectal, intranasal or sublingual formulations have relatively lengthy onset times or erratic absorption characteristics that are not well suited to control acute disorders.

Conditions of acute operative/postoperative or traumatic/ posttraumatic pain as well as pain due to severe disease (e.g. myocardial infarction, nephrolithiasis, etc.) is usually treated with opioid analgesics which are administered parenterally (by intravenous or intramuscular administration) to obtain a rapid onset of analgesia. In such cases, rapid-onset oral alternatives are of considerable therapeutic interest. Also for the treatment of other acute disorders, it is of considerable interest to provide fast-acting therapeutic compositions which may be administered orally or by the intranasal route instead of parenterally or rectally.

However, many pharmaceutically active agents which would be advantageous to administer orally are not suitable to be swallowed. They may, for example, be inactivated by the gastrointestinal liquids, have a slow action because of a low solubility in the aqueous medium, or be highly susceptible to metabolism by gastro-intestinal enzymes and have poor absorption properties, as exemplified for peptide hormones. It is therefore more preferable to arrange for the active component to be taken up through the mucous membranes of the oral or nasal cavity. For the oral cavity, the most preferred way of administration is via the sublingual route. In this administration, a dosage unit of the pharmaceutical composition is placed under the tongue, and the active component is absorbed through the surrounding mucous membranes. However, with this way of administration, the risk that the patient swallows the medication by swallowing saliva is well known.

For the treatment of acute pain may be used fentanyl, N-(1-phenethyl-4-piperidyl)-propioanilide, or one of its pharmaceutically acceptable salts. This compound is an opioid agonist and shares many of the pharmacodynamic effects of opiates such as morphine and meperidine. However, compared to these opiates, fentanyl exhibits little hypnotic activity, rarely induces histamine release, and respiratory depression is more short-lived. Fentanyl is commercially available for intravenous, intrabuccal (lozenge-transmucosal) and transdermal administration.

Following parenteral administration of fentanyl, the analgesic action is more prompt and less prolonged than that of morphine and meperidine. The onset of analgesia following i.v. administration is rapid. Peak analgesia is obtained within a few minutes. Following transbuccal administration by a lozenge, consumption of the lozenge is usually complete within 30 min and peak plasma concentrations appear after around 20 minutes, as described by e.g. Farrar et al., J. Natl. Cancer Inst., 1998, 90(8), p. 611-616. Analgesia is apparent within 5-15 min and peaks at about 20-50 min. While this is an improvement over oral administration for gastrointestinal uptake, a quicker onset of analgesia would be of substantial benefit to the patient. In addition, substantial amounts of lozenge-administered fentanyl are swallowed by the patient. This is not desirable and results in the administration of excessive amounts of the drug, which may give rise to side effects.

### Objects of the invention

It is one object of the invention to provide for the treatment of acute disorders by peroral or intranasal administration of at least one pharmaceutically active agent in a manner giving rise

to pharmacologically effective plasma levels of said agent or agents within a short time after administration.

5 It is another object of the invention to provide a pharmaceutical composition suitable for that purpose.

It is a further object of the invention to provide a method of making such a composition.

10 It is an additional object of the invention to provide a method of manufacture of a medicament for sublingual or intranasal administration containing a physiologically effective dose of at least one pharmaceutically active compound useful in the treatment of acute disorders.

#### 15 **Description of the drawing**

The sole figure of the drawing shows the result of a test of the bioadhesive strength of a composition according to the invention. It is a diagram showing the maximum tensile strength against the concentration.

#### 20 **Summary of the invention**

According to the invention, the peroral treatment of acute disorders comprises sublingual administration of an ordered mixture comprising a pharmacologically effective amount of at least one pharmaceutically active agent. Said agent or agents is administered sublingually in  
25 combination with a bioadhesion and/or mucoadhesion promoting compound. In the same manner, the same composition is also useful for intranasal administration.

Further according to the invention, there is also provided a single-dose pharmaceutical composition for sublingual or intranasal administration, comprising a pharmacologically  
30 effective amount of at least one pharmaceutically active agent. Said composition also contains a bioadhesion or mucoadhesion promoting compound. This composition reduces erratic drug absorption via swallowed saliva and enables the administration of small amounts of said agent or agents. Therefore, it substantially reduces the risk of side effects and inpatient as well as outpatient variation of therapeutic response. Thereby the risk of drug  
35 accumulation is reduced, making the pharmaceutical preparation well suited for repeated dosing in patients suffering from acute disorders.

The amount of active agent or agents contained in the pharmaceutical composition of the invention is obviously dependent on a number of factors, which are to be evaluated by the treating physician. Among such factors may be mentioned the specific agent used and the type of disorder being treated, the medical status of the patient, and others.

5

When fentanyl is used for the treatment of acute or breakthrough pain, the composition of the invention should contain from 0.05 up to 20 weight percent of fentanyl or one of its pharmaceutically acceptable salts. More preferably, the compositions contains from 0.05 to 5 weight percent of fentanyl, and especially from 0.1 to 1 weight percent. The contents can also be expressed as the amount of fentanyl in a dose unit of the composition, such as a tablet. In this case, a dose unit should contain from 0.025 to 10 mg, and preferably 0.05 to 2 mg of fentanyl. When the fentanyl is used in the form of a salt, these percentages and amounts should be recalculated accordingly.

15 Still further according to the invention, the sublingual or intranasal composition comprises an ordered mixture of one or more bioadhesive and/or mucoadhesive carrier substances coated with the pharmaceutically active agent or agents in a fine particulate form. According to the invention, the carrier substance or substances are insoluble or sparingly soluble in water. The term "ordered mixture" is meant to denote the use of a fine particulate quality of active ingredient(s) intimately mixed with coarser excipient particles. Then, the fine drug particles are attached essentially as primary particles on the surface of the excipient (carrier) particles. Also terms like "interactive mixture" or "adhesive mixture" can be used interchangeably, in this context.

25 It is preferred to formulate the composition according to the invention by use of a variant of the technology for formulating rapidly dissolving ordered-mixture compositions disclosed in European patent EP 0 324 725. In these compositions, the drug in a finely dispersed state covers the surface of substantially larger, water-soluble carrier particles. Such compositions disintegrate rapidly in water, thereby dispersing their contents of microscopic drug particles.

30

The dissolution of a fine particulate drug from ordered mixtures has hitherto been associated with the use of soluble carriers. This approach is characterised by a rapid dissolution of the carrier, thus quickly liberating the fine drug particles. These drug particles, now presented as discrete units, will rapidly dissolve, due to favourable hydrodynamics. This approach has previously been limited to the use of large volumes of dissolving fluid. It has been understood that it is only when drug particles are liberated to larger volumes of dissolving liquid that the dissolution is not hindered by saturation phenomenon or unfavourable hydrodynamics.

35

However, in the published PCT application No. WO 00/16750, the use of ordered mixtures with soluble carriers has been applied to sub-lingual administration. In spite of the limited volume of dissolving fluid (saliva) in the oral cavity it was found that a rapid dissolution and subsequent drug uptake could be achieved. It has now, unexpectedly, been realised that also insoluble or sparingly soluble carriers can be used with the same result. It is believed that the optimal exposure of discrete drug particles (i.e. in a non-agglomerated form) on the surface of the coarser carrier particles represents a determining factor for the rapid dissolution. Since the drug is positioned on the surface of the main tablet component, the large surface area taking part in dissolution will give a rapid dissolution in spite of the fact that these drug particles are not liberated from the insoluble carrier, prior to dissolution. Thus, dissolution can rapidly take place also from drug particles attached to a carrier, as long as the drug is in very fine particulate form and present as discrete, non-agglomerated units. Another prerequisite is that the drug is used in low proportions. Preferably the dose should be lower than 10 mg and more preferably lower than 2 mg.

An advantage with insoluble carriers over soluble carriers is their improved tendency to adhere to the mucosa after being coated with a finer, bio/muco-adhesive component. It was found that a soluble carrier, will soon after administration, start to dissolve and thereby the mucoadhesion will decrease. An insoluble carrier coated with bioadhesive particles, on the other hand, will remain attached to the mucosa for a longer time and an improved mucoadhesion will result. This is further explained in Example 1.

A bioadhesion and/or mucoadhesion promoting agent is additionally added to the carrier particles according to the invention. The bioadhesion and/or mucoadhesion promoting agent is effective in making the active agent or agents adhere to the oral or nasal mucosa and may, in addition, possess properties to swell and expand in contact with water. The bio/mucoadhesion promoting agent must then be present on the surface of the carrier particles.

The expression "mucoadhesion" is meant to denote an adhesion to mucous membranes which are covered by mucus, such as those in the oral cavity, while the expression "bioadhesion" is meant to denote an adhesion to biological surfaces more in general, including mucous membranes which are not covered by mucus. These expressions generally overlap as definitions, and may usually be used interchangeably, although the expression "bioadhesive" has a somewhat wider scope. In the present specification and claims, the two

expressions serve the same purpose as regards the objects of the invention, and this has been expressed by the use of the common term "bio/mucoadhesion".

Suitably the carrier particles contain from 0.1 up to 40 weight percent of bio/mucoadhesion promoting compound, based on the total composition. In practice, contents below 1 weight percent have been found to give an insufficient bio/mucoadhesive effect. The preferred range of bio/mucoadhesion promoting agent content is from 2 to 25 weight percent.

It is preferred that the bio/mucoadhesion promoting agent is a polymeric substance, preferably a substance with an average molecular weight above 5,000 (weight average). The level of hydration of the mucosa adhesion promoting agent interface is of importance in the development of bio/mucoadhesive forces. Therefore, the faster the swelling of the polymer, the faster is the initiation of bio/mucoadhesion. The hydration of bioadhesive compounds also makes them useful as absorption enhancers according to the invention.

Preferably, the carrier particle size is less than 750  $\mu\text{m}$ , and more preferably from 50 to 500  $\mu\text{m}$ . Although particle sizes outside the indicated range can be used, practical difficulties are experienced when formulating pharmaceutical preparations from particles having such sizes. The carrier used may comprise any substance which is pharmaceutically acceptable, is insoluble or sparingly soluble in water, and which can be formulated into particles fit for incorporating a bio/mucoadhesion promoting agent. A number of such substances are known to the person skilled in this art. As suitable examples may be mentioned polymers such as celluloses (e.g. micro-crystalline cellulose), cellulose derivatives, starch, starch derivatives, cross-linked polymers based on e.g. starch, cellulose and polyvinylpyrrolidone. Furthermore, inorganic salts can be used, such as calcium phosphate, dicalcium phosphate hydrate, dicalcium phosphate dihydrate, tricalcium phosphate, calcium carbonate, and barium sulfate. Mixtures or co-processed qualities of the above-mentioned materials may also be used.

In accordance with one particularly preferred aspect of the invention, the carrier also possesses fragmenting behaviour. By fragmentation behaviour is meant that the carrier is to some extent a brittle material which is readily crushed or broken up when a pharmaceutical composition of which it forms a part is compacted into tablets. This effect is especially pronounced when the bio/mucoadhesion promoting agent also serves as a disintegrant. Dicalcium phosphates have been found to be particularly suitable as fragmentation promoting agents.



The addition of a pharmaceutically acceptable surfactant to the composition is also a preferred feature of the invention. The increased wetting effect of the surfactant enhances the wetting of the carrier particles, which results in faster initiation of the bio/mucoadhesion. The surfactant should be in a finely dispersed form and intimately mixed with the active agent  
5 or agents. The amount of surfactant should be from 0.5 to 5 weight percent of the composition, and preferably then from 0.5 to 3 weight percent.

As examples of suitable surfactants may be mentioned sodium lauryl sulfate, polysorbates, bile acid salts and mixtures of these.

10

A variety of polymers known in the art can be used as bio/mucoadhesion promoting agents. In addition to their polymeric nature, their ability to swell is important. On the other hand, it is also important that they are substantially insoluble in water. Their swelling factor by volume when brought into contact with water or saliva should preferably be at least 10, while a factor  
15 of at least 20 is more preferred. Examples of such bio/mucoadhesion promoting agents include cellulose derivatives such as hydroxypropylmethyl cellulose (HPMC), hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), methyl cellulose, ethyl hydroxyethyl cellulose, carboxymethyl cellulose and sodium carboxymethyl cellulose (NaCMC); starch derivatives such as moderately cross-linked starch; acrylic polymers such as carbomer and  
20 its derivatives (Polycarbophyl, Carbopol®, etc.); polyethylene oxide (PEO); chitosan (poly-(D-glucosamine)); natural polymers such as gelatin, sodium alginate, pectin; scleroglucan; xanthan gum; guar gum; poly co-(methylvinyl ether/maleic anhydride); and crosscaramellose. Combinations of two or more bio/mucoadhesive polymers can also be used. More generally, any physiologically acceptable agent showing bio/mucoadhesive characteristics may be used  
25 successfully to be incorporated in the carrier. Bio/mucoadhesiveness can be determined in vitro, e.g. according to G. Sala et al., Proceed. Int. Symp. Contr. Release. Bioact. Mat. 16:420, 1989.

Some suitable commercial sources for representative bio/mucoadhesive polymers include:

30

Carbopol® acrylic copolymer - BF Goodrich Chemical Co, Cleveland, OH, USA;  
HPMC - Dow Chemical Co., Midland, MI, USA;  
NEC (Natrosol) - Hercules Inc., Wilmington, DE., USA;  
HPC (Klucel®) - Dow Chemical Co., Midland, MI, USA;  
35 NaCMC - Hercules Inc. Wilmington, DE., USA;  
PEO - Aldrich Chemicals, USA;  
Sodium Alginate, - Edward Mandell Co., Inc., Carmel, NY, USA;

Pectin - BF Goodrich Chemical Co., Cleveland, OH, USA.'

Ac-Di-Sol® (modified cellulose gum with a high swellability) - FMC Corp., USA;

Actigum, - Mero-Rousselot-Satia, Baupre, France;

Satiaxane - Sanofi BioIndustries, Paris, France;

5 Gantrez® - ISP, Milan, Italy;

Chitosan - Sigma, St Louis, MS, USA;

Depending on the type and the proportion of the bio/mucoadhesion promoting agent used, the rate and intensity of bio/mucoadhesion may be varied. According to one of the preferred  
10 aspects of the invention, substances with high and rapid capacity for swelling are preferred.

In order for the pharmaceutical composition of the invention to function properly when a bio/mucoadhesion promoting agent is added thereto, this agent must be positioned at the surfaces of the carrier particles. The bio/mucoadhesion promoting agent can then be  
15 admixed to the carrier particles in several ways. In a preferred embodiment of the invention, a fine particulate quality of the bio/mucoadhesion promoting agent is mixed together with the coarse carrier for a sufficient time to produce an ordered mixture, where the finer particles exist as discrete primary particles adhered to the surfaces of the carrier particles. Thus, the bio/mucoadhesion promoting agent is admixed in the same way as the active compound  
20 described in European patent No. 0 324 725.

The bio/mucoadhesion promoting agent suitably has a particle size between 1 and 100 µm. When the particles of this agent are to be mixed with the carrier particles to form an ordered mixture, their size lies within the lower part of the size interval, and suitably their size is then  
25 below 10 µm.

The invention is particularly directed to the administration of drugs which are used for the treatment of medical conditions where a rapid and transient effect is desirable, such as pain, insomnia, allergic conditions and pulmonary oedema. As non-limiting examples of such  
30 drugs may be mentioned morphine (analgetic), fentanyl (analgetic), alfentanyl (analgetic), sufentanyl (analgetic), buprenorphine (analgetic), pizotifen (analgetic), sumatriptan (analgetic), indomethacin (analgetic), sulindac (analgetic), diclofenac (analgetic), ketorolac (analgetic), piroxicam (analgetic), tenoxicam (analgetic), ibuprofen (analgetic), naproxen (analgetic), ketoprofen (analgetic), butazolidine (analgetic), phenylbutazone (analgetic),  
35 diazepam (insomnia), oxazepam (insomnia), zopiclone (insomnia), zolpidem (insomnia), propiomazin (insomnia), valeriana (insomnia), levomepromazin (insomnia), cyclizine

(allergy), cetirizine (allergy), terfenadine (allergy), acrivastine (allergy), fexofenadine (allergy) and furosemide (diuretic).

5 Other drugs which benefit from an enhanced absorption and which may be used for medical conditions where a rapid onset of the action is desirable include, without any limiting sense, various peptides and enzymes, such as atrial natriuretic peptides (ANP, ANF, auriculin) (diuretics), brain natriuretic peptides (diuretics), platelet aggregation inhibitors (anticoagulants), streptokinase (anticoagulant), heparin (anticoagulant), urokinase (anticoagulant), renin inhibitors (hypertension), insulin (antidiabetic), and sleep inducing  
10 peptide (insomnia).

Further examples of drugs where exposure to gastric acid has to be avoided and where the swallowing of active drug containing saliva can be minimised by means of the bio/mucoadhesive properties of the present formulations include, without any limiting sense,  
15 benzimidazole derivatives used as  $H^+$ ,  $K^+$  and ATPase inhibitors (gastric acid reduction), such as omeprazole, pantoprazole, perprazole and lansoprazole. Other  $H^+$ ,  $K^+$  and ATPase inhibitors include allyl isothiocyanate, trifluorperazide, nolinium bromide, RP 40749 and fenoctimine.

20 The invention is particularly suitable for the administration of fentanyl and its pharmacologically acceptable salts, such as the citrate or maleate, which are not readily soluble in water. The particles of fentanyl or salt thereof will suitably have a maximum particle size of about 24  $\mu m$  but will preferably not be greater than about 10  $\mu m$ . Fentanyl is caused to adhere to the carrier particles e.g. by dry mixing of the ingredients during a period  
25 of time of sufficient length. This time period can vary according to the mixing equipment used. A person skilled in the art will have no difficulty in determining by experimentation a suitable mixing time for a given combination of active substance, bio/mucoadhesion promoting agent, and carrier, by using a particular mixing equipment.

30 A further preferred aspect of the invention comprises the incorporation of a disintegrating agent in the composition of the invention. Such an agent which will accelerate the dispersion of the carrier particles. Examples of disintegrating agents according to the invention include cross-linked polyvinylpyrrolidone, carboxymethyl starch, natural starch, microcrystalline cellulose, cellulose gum and mixtures of these. A preferred content of disintegrating agent is  
35 from 1 % to 10 % of the composition. As can be seen, the definitions of the disintegrating agent and the bio/mucoadhesion promoting agent overlap somewhat, and it may be preferred that both functions are served by the same substance. However, it is important to

note that these two categories of excipients are not equivalent, and there are efficiently functioning disintegrants which do not possess bio/mucoadhesive properties, and vice versa.

The ordered mixtures prepared in accordance with the present invention can be used as such for intranasal administration. Normally the powder mixture is then insufflated to the nasal cavity by the aid of some type of delivery device. The ordered mixture can also be incorporated into various kinds of pharmaceutical preparations intended for sublingual administration. Irrespective of the form given to the preparation, it is important that the preparation is essentially free from water, since its bio/mucoadhesion promoting character results from its practically instantaneous hydration when brought into contact with water or saliva. Premature hydration would drastically decrease the mucoadhesion promoting properties and result in a premature dissolution of the active substance.

A pharmaceutical composition for the preferred sublingual route of administration can be obtained by combining an aforementioned ordered mixture with conventional pharmaceutical additives and excipients used in the art for sublingual preparations. Appropriate formulation methods are well known to the person skilled in the art; see, for instance, Pharmaceutical Dosage Forms: Tablets. Volume 1, 2nd Edition, Lieberman H A et al.; Eds.; Marcel Dekker, New York and Basel 1989, p. 354-356, and literature cited therein. Suitable additives comprise additional carrier agents, preservatives, lubricants, gliding agents, disintegrants, flavorings, and dyestuffs.

Thus, the invention provides a dosage form which is easy and inexpensive to manufacture, enables rapid active substance release, promotes a rapid uptake of the active agent or agents through the oral or nasal mucosa, and enhances the uptake of otherwise poorly soluble substances, such as peptides.. The use of a low dose of active agent is provided for, supporting a short duration of action while enabling a repeated dosing schedule for patients in need of treatment of recurrent acute disorders.

The invention will now be illustrated in more detail by reference to examples.

### **Example 1**

#### **Materials**

Dibasic calcium phosphate dihydrate (DCP) (Emcompress, Edward Mendell Co, Inc, USA) with low aqueous solubility and Mannitol (granulated quality, Roquette, France) with high aqueous solubility were used as non-bioadhesive carrier materials in the preparation of

ordered mixtures. A size fraction of 180-355  $\mu\text{m}$  for each material was obtained by dry sieving (Retsch, Germany).

Cross-linked carboxymethyl cellulose sodium (Ac-Di-Sol, FMC, Cork, Ireland) were used in a fine divided form to represent a material with mucoadhesive/bioadhesive properties. The fine particle size fraction of Ac-Di-Sol was obtained by milling in a mortar grinder (Retsch, Germany) followed by air classification (100 MZR, Alpine, Germany).

#### Primary characterisation of test materials

All powders were stored at 40% RH and room temperature, for at least 48 hours before characterisation and mixing. The external surface area of the coarser size fractions (180- 355  $\mu\text{m}$ ) of Mannitol and DCP was determined using Friedrich permeametry ( $n=3$ ) (Eriksson et al 1990). Blaine permeametry was used to determine the external surface area of the Ac-Di-Sol powder (Alderborn et al 1985) (Table 1).

#### Preparation of ordered/interactive mixtures

Milled Ac-Di-Sol (Table 1) was added to Mannitol or DCP (both 180-355  $\mu\text{m}$ ) in varying proportions to obtain different concentrations of Ac-Di-Sol. The powders were mixed in glass jars in a 2L Turbula mixer (W.A. Bachofen AG, Basel, Switzerland) at 120 rpm for 24 hours. Mixing was performed in accordance with previous studies (Westerberg 1992; Sundell-Bredenberg and Nyström 2001) and the mixture homogeneity was visually confirmed.

#### Measurements of bioadhesive/mucoadhesive properties

##### Materials and characterisation of the mucosa

Fresh pig intestine was collected at a slaughterhouse (Swedish Meat AB, Uppsala, Sweden) and used fresh or was frozen until required. Before use, the frozen intestine was thawed in buffer solution at 4°C overnight. The buffer solution used was Krebs-Ringer Bicarbonate (Sigma-Aldrich Chemie GmbH, Steinheim, Germany) with a pH of 7.4.

To test the quality of the mucus layer and the effect of handling the mucosa, several tissue specimens were stained with Alcian blue, partly according to the method by Corne et al (1974). Both fresh and frozen tissues were then soaked for two hours in TRIS (TRIZMAHydrochloride, Sigma-Aldrich Chemie GmbH, Steinheim, Germany) buffered sucrose solution (Sigma-Aldrich Chemie GmbH, Steinheim, Germany) with Alcian blue 8 GX, (Certistain, Merck, Germany) (1mg/ml). The tissues were rinsed in TRIS/sucrose buffer and visually studied. On evaluating the quality of the mucus layer and the effect of handling

the tissue, it was noted that neither the thawing process (in buffer solution at 4 °C) nor handling affected the quality of the mucosa, i.e. the mucus layer remained intact, and therefore both fresh and frozen mucosa were used in this study.

5

### **Adhesion test**

A TA-HDi texture analyser (Stable Micro Systems, Haslemere, UK) with a 5 kg load cell and associated software was used for the bioadhesion studies. The pig intestine was cut into approximately 2 cm<sup>2</sup> pieces and placed in a tissue holder. The powder mixtures [using double-sided tape (Scotch, 3M Svenska AB, Sollentuna, Sweden)] was attached to the upper probe. The application of the powder mixtures was performed by immersing the probe in to a powder bed and there after the probe was gently shaken to remove any excess, in order to achieve a monolayer of particles, which was visually validated. After spreading 30 µl of buffer with a pipette on the mucosa to standardise hydration, the studied material was brought into contact with the mucosa under a force of 0.5 N over 30 seconds. The probe was then raised at a constant speed of 0.1 mm/s and the detachment force was recorded as a function of displacement. The detachment force was measured at a sampling rate of 25 measurements/second throughout the measuring cycle. The maximum force monitored, i.e. the fracture force, was determined using the computer software Texture Expert Exceed (Stable Microsystems, Haslemere, UK). The tensile stress (N/cm<sup>2</sup>) was obtained by dividing the detachment force by the area of the probe.

### **Results regarding the use of ordered/interactive mixtures (the addition of fine bioadhesive particles) to increase the bioadhesive properties of a carrier material**

#### **The effect of the amount of bioadhesive/mucoadhesive component**

Tensile stress between the mucosa and the non-bioadhesive carrier particles were improved ( $p < 0.0001$ ) when the coarse DCP or Mannitol was mixed with the fine particle size of Ac-Di-Sol (Fig. 1). The bioadhesive properties improved ( $p < 0.05$ ) initially with increases in the concentration of Ac-Di-Sol.

30

Ordered mixtures of DCP containing the two highest concentrations of Ac-Di-Sol (28.2 and 39.3% w/w) gave values for tensile stress significantly higher ( $p < 0.05$ ) than for powders of pure Ac-Di-Sol (Fig. 1). This effect was however not seen ( $p > 0.1$ ) with mixtures containing Mannitol, probably because of the higher water solubility of Mannitol, as discussed below.

35

As seen in Fig. 1, the increase in bioadhesive strength is significant ( $p < 0.01$ ) up to a certain amount of added Ac-Di-Sol. When the amount exceeded approximately 20% w/w, the significant increase ( $p > 0.1$ ) in tensile stress.

### The effect of carrier solubility

DCP mixtures were significantly more ( $p < 0.02$ ) bioadhesive (had higher tensile stress than Mannitol mixtures). This may be a result of the higher water solubility of Mannitol. Thus, the fracture for the Mannitol mixtures might have gone through dissolved peripheral regions of the interactive mixtures and not entirely through the mucus layer.

**Table 1. Primary characteristics of test materials. Mean values ( $\pm$  s.d.).**

Material	Particle size fraction ( $\mu\text{m}$ )	Apparent particle density ( $\text{g}/\text{cm}^3$ ) <sup>a</sup>	External specific surface area ( $\text{cm}^2/\text{g}$ ) <sup>b</sup>
Ac-Di-Sol	Milled	1.607 ( $\pm 0.001$ )	6400 ( $\pm 91$ ), 6700 ( $\pm 180$ )
Mannitol	180-355	1.486 ( $\pm 0.000$ )	290 ( $\pm 6.5$ )
DCP	180-355	2.884 ( $\pm 0.001$ )	440 ( $\pm 3.7$ )

<sup>a</sup> Measured with a helium pycnometer (AccuPyc 1330 Pycnometer, Micromeritics, USA) ( $n=3$ ).

<sup>b</sup> Measured with a Friedrich permeameter (Eriksson et al 1990) or Blaine permeameter (Alderborn et al 1985) ( $n=3$ ).

### **Conclusions**

The tensile stress between the mucosa and the coarser Mannitol or DCP powders were improved ( $p < 0.0001$ ) when these were mixed with the fine particulate Ac-Di-Sol. This indicates that addition of materials with a higher adhesion tendency will increase the adhesion of another, less bioadhesive material, such as the carrier materials.

The use of interactive mixtures of bioadhesive powders with aqueous-insoluble carriers rather

than with aqueous-soluble carriers is unexpectedly superior, especially at a proportion close to monoparticulate surface coverage.

Thus, it is concluded that such interactive mixtures, using sparingly soluble carriers, is an

interesting formulation tool in the development of bioadhesive formulations such as instant release formulations for sublingual administration.

**Example 2. Preparation of a rapidly disintegrating tablet with bio/mucoadhesion promoting properties.**

A batch of 1000 tablets was produced from the following compositions: 82.5 g of dibasic calcium phosphare dihydrate (DCP) having a particle size from about 250 to 450 microns, was mixed with 500 mg of micronized fentanyl over a period of 50 hours. The resulting mixture was admixed with 10.0 g micronised sodium alginate (bio/mucoadhesion promoting agent) over a period of 5 hours. Thereafter, 5.0 g of Avicel® Ph 101 (acting as binder) and 2.0 g of Ac-Di-Sol® (modified cellulose gum acting as effective disintegrant) was admixed for 60 minutes. The resulting mixture was mixed with 0.5 g magnesium stearate (lubricant) for 2 minutes and the final tablet mass was then compacted into tablets at a compaction pressure of 200 MPa, each tablet having a weight of 100 mg and containing 0.5 mg of fentanyl.

**Example 3. Preparation of rapidly disintegrating tablets for the administration of atrial natriuretic peptide (ANP)**

Rapidly disintegrating tablets with bio/mucoadhesive properties which in addition enhance absorption of large molecules in sublingual administration were prepared according to Example 2, each tablet containing 0.7 mg ANP. However, in this composition the sodium alginate was removed and the addition of Ac-Di-Sol® was increased to 5.0 g, now acting as both disintegrant and bioadhesive component. The tablets show a rapid release of ANP and an enhanced uptake of ANP through the oral mucosa in comparison with conventional peroral formulations. The preparation may be used for the treatment of pulmonary edema.

**Example 4. Preparation of rapidly disintegrating tablets for the administration of omeprazole**

Rapidly disintegrating tablets with bio/mucoadhesive properties for sublingual administration were prepared according to example 3, each tablet containong 10 mg of omeprazole. The tablets show a rapid release of omeprazole and an enhanced uptake of omeprazole through the oral mucosa, as well as a reduced swallowing of omeprazole in the saliva, in comparison with conventional peroral formulations. The preparation may be used for the treatment of



gastroesophageal reflux.

**Example 5. Preparation of an intranasal powder of atrial natriuretic peptide (ANP)**

5 Ordered mixtures with bio/mucoadhesive properties for intranasal administration were prepared according to example 2, each dosed volume of powder mixture containing 0.7 mg of ANP. In contrast to the composition of example 2, no tablets were compressed and subsequently no addition of binder (Avicel® Ph 101), disintegrant (Ac-Di-Sol®) nor lubricant (magnesium stearate) was made. After insufflation into the nasal cavity the powder showed a  
10 rapid dissolution of ANP and an enhanced uptake of ANP through the nasal mucosa in comparison with conventional peroral formulations. The preparation may be used for the treatment of pulmonary edema.

In the foregoing specification, the present invention has been described with reference to  
15 various examples and preferred embodiments. However, for a person skilled in the art, it is clear that the scope of the invention is not limited to these examples and embodiments, and that further modifications and variations are possible without departing from the inventive idea. The scope of the invention is thus only limited by the appended claims.

20 **References**

Alderborn, G., Pasanen, K., Nyström, C. (1985) Studies on direct compression of tablets. XI. Characterization of particle fragmentation during compaction by permeametry measurements of tablets. *Int. J. Pharm.* **23**: 79-86

25

Corne, S.J., Morrisey, S.M., Woods, R.J. (1974) A method for the quantitative estimation of gastric barrier mucus. *J. Physiol.* **242**: 116P-117P

30

Eriksson, M., Nyström, C., Alderborn, G. (1990) Evaluation of a permeametry technique for surface area measurements of coarse particulate materials. *Int. J. Pharm.* **63**: 189-199

Sundell-Bredenberg, S., Nyström, C. (2001) The possibility of achieving an interactive mixture with high dose homogeneity containing an extremely low proportion of a micronised drug. *Eur. J. Pharm. Sci.* **12**: 285-295

35

Westerberg, M. (1992) Studies on ordered mixtures for fast release and dissolution of drugs with low aqueous solubility. Ph.D. Thesis. Uppsala University, Reprocentralen, HSC, Uppsala, Sweden

### Claims

1. A pharmaceutical composition for the treatment of acute disorders by sublingual  
5 or intranasal administration, comprising an essentially water-free, ordered mixture of  
microparticles of at least one pharmaceutically active agent adhered to the surfaces of carrier  
particles, said particles being substantially larger than said microparticles and being insoluble  
or sparingly soluble in water, and a bioadhesion and/or mucoadhesion promoting agent  
adhered to the surface of the carrier particles.
- 10 2. A composition according to claim 1, wherein the microparticles of said active  
agent or agents have a weight based mean diameter of less than 10  $\mu\text{m}$ .
3. A composition according to claim 1 or 2, wherein the mean sieve diameter of the  
15 carrier particles is less than 750  $\mu\text{m}$ , preferably then from 50 to 500  $\mu\text{m}$ .
4. A composition according to any one of claims 1-4, wherein the carrier particles  
comprise a brittle material which will fragmentize easily when compressed.
- 20 5. A composition according to any one of claims 1-4, wherein the carrier particles  
contain from 0.1 to 40 weight percent of the bio/mucoadhesion promoting agent, preferably  
then from 2 to 25 weight percent, based on the total composition.
- 25 6. A composition according to claim 5, wherein the bio/mucoadhesion promoting  
agent is selected from the group consisting of cross-linked polymers, acrylic polymers,  
cellulose derivatives, natural polymers having bio/mucoadhesive properties, and mixtures  
thereof.
- 30 7. A composition according to claim 6, wherein the bio/mucoadhesion promoting  
agent is selected from the group consisting of cellulose derivatives and comprising  
hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, sodium  
carboxymethyl cellulose, methyl cellulose, ethyl hydroxyethyl cellulose, carboxymethyl  
cellulose and modified cellulose gum; crosscaramellose; modified starch; acrylic polymers  
comprising carbomer and its derivatives; polyethylene oxide; chitosan; gelatin; sodium  
35 alginate; pectin; scleroglucan; xanthan gum; guar gum; poly-co-(methyl vinyl ether-maleic  
anhydride); and mixtures thereof.

8. A composition according to any one of claims 1-7, further comprising a pharmaceutically acceptable surfactant in a finely dispersed form and intimately mixed with the active agent or agents.

5

9. A composition according to claim 8, wherein the surfactant is present in an amount from 0.5 to 5 weight percent of the composition, preferably then 0.5 to 3 weight percent.

10

10. A composition according to claim 8 or 9, wherein the surfactant is selected from the group consisting of sodium lauryl sulfate, polysorbates, bile acid salts and mixtures thereof.

15

11. A composition according to any one of claims 1-10, wherein the carrier particles comprise at least one material selected from the group consisting of pharmaceutically acceptable polymers, pharmaceutically acceptable inorganic salts and mixtures or co-processed qualities of these materials

20

12. A composition according to claim 11, wherein the carrier particles comprise at least one of the materials selected from the group consisting of cellulose, cellulose derivatives, starch, starch derivatives, cross-linked polymers based on starch or cellulose, or polyvinylpyrrolidone.

25

13. A composition according to claim 11, wherein said inorganic salt is selected from the group consisting of calcium phosphate, dicalcium phosphate dihydrate, dicalcium phosphate dihydrate, tricalcium phosphate, calcium carbonate and barium sulfate.

30

14. A sublingual composition according to any one of claims 1-13, wherein the composition contain at least one pharmaceutical disintegrating agent promoting the dispersion of the carrier particles with the admixed active agent or agents, over the sublingual mucosa.

35

15. A sublingual composition according to claim 14, wherein the disintegrating agent is selected from the group consisting of cross-linked polyvinylpyrrolidone, carboxymethyl starch, natural starch, microcrystalline cellulose, cellulose gum, and mixtures thereof.

16. A sublingual composition according to claim 14 or 15, wherein the disintegrating agent is present in an amount from 1 to 10 weight percent of the composition.

17. A composition according to any one of claims 1-16, wherein the  
5 pharmaceutically active agent is fentanyl or a pharmaceutically acceptable salt thereof.

18. A composition according to any one of claims 1-17, for the treatment of acute disorders by sublingual administration.

10 19. A composition according to claim 18, for the treatment of acute or breakthrough pain by sublingual administration of fentanyl or a pharmaceutically acceptable salt thereof.

20. A composition according to any one of claims 1-13 or 17, for the treatment of acute disorders by intranasal administration.

15

21. A composition according to claim 20, for the treatment of acute or breakthrough pain by intranasal administration of fentanyl or a pharmaceutically acceptable salt thereof.

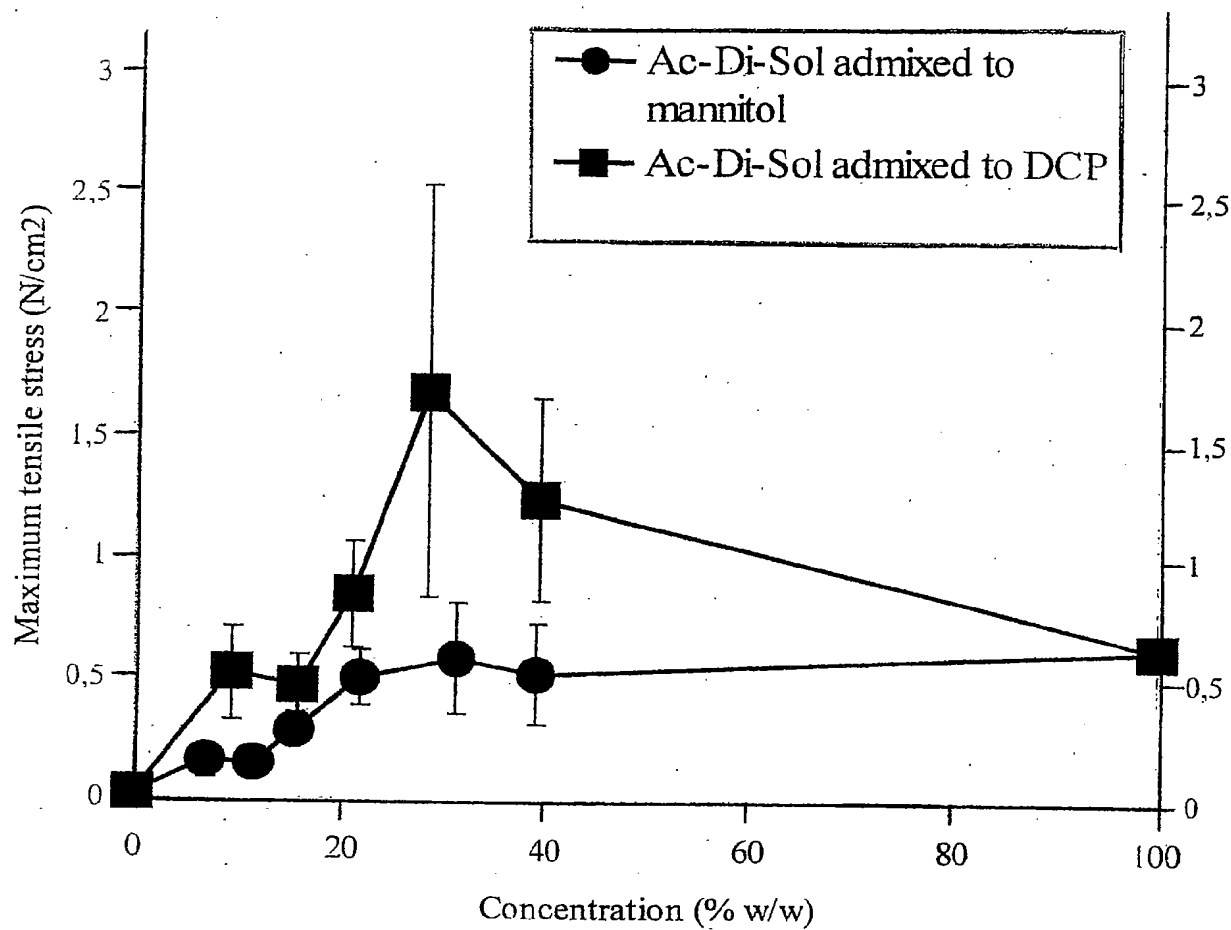
20 22. A method for the treatment of acute disorders, wherein to an individual afflicted with said disorder is administered sublingually or intranasally at least one dose unit of an essentially water-free pharmaceutical composition containing an effective amount of at least one pharmaceutically active agent in the form of microparticles adhered to the surfaces of carrier particles, which are substantially larger than said microparticles and are essentially water-insoluble or sparingly water-soluble, and a bioadhesion and/or mucoadhesion  
25 promoting agent adhered to the surface of the carrier particles.

23. A method according to claim 22, wherein the pharmaceutically active agent is fentanyl or a pharmaceutically acceptable salt thereof.

30 24. A method according to claim 23, wherein the fentanyl is administered in an amount from 0.025 to 10 mg, preferably then from 0.05 to 2 mg, per dose unit.

-----

1/1



Maximum tensile stress in detaching powder specimens from mucus membrane as a function of concentration of milled Ac-Di-Sol mixed with Mannitol or DCP. Mean values  $\pm$  S.D.

FIG. 1

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 2004/000037

## A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 31/4468

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-INTERNAL, WPI DATA, FULLTEXT, MEDLINE, BIOSIS

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 0016750 A1 (DIABACT AB), 30 March 2000 (30.03.2000) --	1-24
A	EP 0681833 A2 (DOTT RESEARCH LABORATORY), 15 November 1995 (15.11.1995), page 4, line 7 - line 11 --	1-24
P,X	European Journal of Pharmaceutical Sciences, Volume 20, 2003, Susanne Bredenberg et al, "In vitro and in vivo evaluation of a new sublingual tablet system for rapid oromucosal absorption using fentanyl citrate as the active substance", pages 327-334, page 331, column 2, lines 12-28 --	1-24

☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

\* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

28 April 2004

Date of mailing of the international search report

2004-05-03

Name and mailing address of the ISA/  
Swedish Patent Office  
Box 5055, S-102 42 STOCKHOLM  
Facsimile No. +46 8 666 02 86

Authorized officer

PATRICK ANDERSSON/BS  
Telephone No. +46 8 782 25 00

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/SE 2004/000037

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	<p>Journal of Pharmacy and Pharmacology, Volume 55, 2003, Susanne Bredenberg et al, "In-vitro evaluation of bioadhesion in particulate systems and possible improvement using interactive mixtures", pages 169-177</p> <p style="text-align: center;">-- -----</p>	1-24



# INTERNATIONAL SEARCH REPORT

International application No.  
**PCT/SE2004/000037**

## Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: **22-24**  
because they relate to subject matter not required to be searched by this Authority, namely:  
**see extra sheet**
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/SE2004/000037

### Box II.1

Claims 22-24 relate to methods of treatment of the human or animal body by surgery or by therapy/diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

31/03/2004

International application No.

PCT/SE 2004/000037

WO	0016750	A1	30/03/2000	AU	764346	B	14/08/2003
				AU	6492799	A	10/04/2000
				BG	105379	A	31/12/2001
				BR	9913945	A	12/06/2001
				CA	2345121	A	30/03/2000
				CN	1326340	T	12/12/2001
				CZ	20011029	A	15/08/2001
				EE	200100182	A	15/08/2002
				EP	1115383	A	18/07/2001
				HU	0103856	A	28/02/2002
				IL	142135	D	00/00/0000
				JP	3381220	B	24/02/2003
				JP	2002526439	T	20/08/2002
				NO	20011473	A	23/05/2001
				NZ	510284	A	30/05/2003
				PL	347126	A	25/03/2002
				RU	2193879	C	10/12/2002
				SE	9803240	D	00/00/0000
				SK	283302	B	02/05/2003
				SK	4022001	A	06/11/2001
				TR	200100855	T	00/00/0000
-----							
EP	0681833	A2	15/11/1995	AT	201982	T	15/06/2001
				CN	1076624	B	26/12/2001
				CN	1117874	A	06/03/1996
				DE	69521239	D, T	20/09/2001
				ES	2158012	T	01/09/2001
				JP	3414539	B	09/06/2003
				JP	8027031	A	30/01/1996
				US	5603943	A	18/02/1997
-----							